

Exhibit 7



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A META-ANALYTICAL APPROACH EXAMINING THE POTENTIAL RELATIONSHIP BETWEEN TALC EXPOSURE AND OVARIAN CANCER

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The concern that use of talc or talc-containing substances in the perineal region of women may subject them to an increased risk for ovarian cancer has become an important issue in the study of ovarian cancer. The purpose of this paper is to examine whether this concern, heightened by several epidemiological studies purporting to show an increased risk, is valid. Epidemiological studies examining the possibility of this relationship are reviewed, and meta-analyses of their results are performed. The conclusion reached herein is that the evidence regarding the risk of ovarian cancer associated with talc exposure is equivocal, and further examination of the relationship is required before a sound conclusion can be made.

INTRODUCTION

There has been recent concern that women's use of talc or talc-containing substances in their perineal region puts them at an increased risk for ovarian cancer. This concern has been brought to the forefront by several case-control studies assessing the risk of ovarian cancer associated with perineal talc use. The purpose of this paper is to review, summarize, and pool these studies in order to document any possible association between an increased risk of ovarian cancer and perineal talc use.

Initially, studies were identified using the MEDLINE database and keying on the terms "ovarian cancer" and "talc or cosmetic." Other studies were identified from the references of these studies. To our knowledge the following ten articles are all the published epidemiological studies that address the purported association between talc use and an increased risk of ovarian cancer: Cramer et al. (1982); Hartge et al. (1983); Whittemore et al. (1988); Booth et al. (1989); Harlow and Weiss (1989); Chen et al. (1992); Harlow et al. (1992); Rosenblatt et al. (1992); Hankinson et al. (1993); and Tzonou et al. (1993). Hankinson et al. (1993) describe a prospective study; the other nine papers describe case-control studies. Table 1 shows the frequency distributions, type of controls, matching factors

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2. Abbreviations: CI, confidence interval; RR, relative risk.

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TABLE 1. Sample Sizes and Characteristics for the Case-Control Studies

Study		Exposed	Unexposed	Type of Controls	Matching Factors for Controls	Location	Type of tumor
CRAM <i>N</i> = 430	Cases	92	123	Population	Precinct of residence, race, and age	Boston, MA	Malignant and borderline
	Controls	61	154				
HART <i>N</i> = 293	Cases	54	77	Hospital	Age, race, and hospital frequencies (unmatched)	Washington, DC	Malignant
	Controls	78	84				
WHIT <i>N</i> = 726	Cases	84	103	Hospital and population	Age, race, hospital, and date of admission	San Francisco, CA	Malignant
	Controls	219	320				
BOOT <i>N</i> = 651	Cases	141	76	Hospital	Age frequency (unmatched)	London and Oxford, England	Malignant
	Controls	256	178				
HAR1 <i>N</i> = 274	Cases	49	67	Population	Age and county of residence frequencies (unmatched)	Seattle, WA	Borderline
	Controls	64	94				
HAR2 <i>N</i> = 474	Cases	114	121	Population	Precinct of residence, age, and race	Boston, MA	Malignant
	Controls	94	145				
ROSE <i>N</i> = 122	Cases	67	40	Hospital	Race and date of diagnostic admission (<i>a posteriori</i>); two cases per control	Baltimore, MD	Malignant
	Controls	10	5				
CHEN <i>N</i> = 336	Cases	7	105	Population	Neighborhood and age	Beijing, China	Malignant
	Controls	5	219				
TZON <i>N</i> = 389	Cases	6	183	Hospital visitors	Hospital ward	Athens, Greece	Malignant
	Controls	7	193				

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for controls, location, and tumor type considered for the case-control studies. Table 2 shows the crude and adjusted relative risks (RR) and confidence intervals (CI) for the case-control studies.

TABLE 2. Relative Risks for the Case-Control Studies

Study	Crude RR (95% CI)	Adjusted RR (95% CI)	Adjusting Factors
CRAM	1.89 (1.27–2.82)	1.61 (1.04–2.49)	Religion, marital status, education, ponderal index, age at menarche, parity, oral contraceptive or menopausal hormone use, and smoking
HART	0.76 (0.47–1.20)	0.7 (0.4–1.1)	Race, age, and gravidity
WHIT	1.19 (0.85–1.66)	1.40 (0.98–1.98)	Parity
BOOT	1.29 (0.92–1.81)	none available	
HAR1	1.07 (0.66–1.75)	1.1 (0.7–2.1)	Age, parity, and use of oral contraceptives
HAR2	1.45 (1.01–2.09)	1.5 (1.0–2.1)	Parity, education, marital status, religion, use of sanitary napkins, douching, age, and weight
ROSE	0.84 (0.27–2.63)	none available	
CHEN	2.92 (0.81–10.88)	3.9 (0.9–10.6)	Education and parity
TZON	0.90 (0.30–2.74)	1.05 (0.28–3.98)	Age, education, weight, age at menarche, menopausal status and age at menopause, parity and age at first birth, smoking, coffee drinking, alcohol consumption, hair dyeing, use of analgesics, use of tranquilizers, and mutual confounding influences

REVIEW OF THE EPIDEMIOLOGICAL STUDIES

In order to describe the ten epidemiological studies, the following abbreviations for the individual studies are used: CRAM — Cramer et al. (1982), HART — Hartge et al. (1983), WHIT — Whittemore et al. (1988), BOOT — Booth et al. (1989), HAR1 — Harlow and Weiss (1989), HAR2 — Harlow et al. (1992), ROSE — Rosenblatt et al. (1992), HANK — Hankinson et al. (1992), CHEN — Chen et al. (1992), and TZON — Tzonou et al. (1993). Each study is summarized according to the following outline: objective, methods, results, and conclusions.

While case-control studies generally produce odds ratios, not relative risks, the purpose of the odds ratio is to estimate the relative risk. Therefore, in this paper the odds ratios are referred to as relative risks; the reader should remember that the values are actually just estimates of the true relative risks.

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1. *CRAM*

Objective. To study whether there is an association between exposure to certain hydrous magnesium silicates, such as talc and asbestos, and the incidence of ovarian cancer.

Methods. Originally, 297 cases were thought to be eligible, among whom 215 cases were ultimately selected to participate. The study was restricted to English-speaking residents of Massachusetts whose ages varied between 18 and 80 at the study's inception. The selected 215 cases were all Caucasians with epithelial cancers, including 39 with tumors of borderline malignancy. Population-based matched controls were randomly selected. The final control group consisted of 215 women out of a potential of 475 controls. Stratification and conditional logistic regression were used to accommodate confounders.

Results. Overall, 42.8% of cases and 28.4% of controls reported exposure to talc via direct application to the perineum, by dusting sanitary napkins with talc, or both. The crude relative risk of ovarian cancer for women with any perineal exposure as opposed to women with no perineal exposure was 1.89 (95% CI 1.27–2.82). Women who used talc on both the perineum and sanitary napkins had an adjusted relative risk of 3.28 (95% CI 1.68–6.42). Finally, the adjusted relative risk for women with any exposure was 1.61 (95% CI 1.04–2.49).

Conclusions. The study provides some support for an association between talc and ovarian cancer, hypothesized because of the similarity of ovarian cancer to mesotheliomas and the chemical relation of talc to asbestos, a known cause of mesotheliomas. While this study made a thorough investigation of the association between perineal talc use and an increased risk of epithelial ovarian cancer, some study weaknesses that preclude the existence of a causal relationship are that no dose-response or duration data were reported, and while a major strength of the study is the use of neighborhood controls, this strength is somewhat tempered by the high nonparticipation rate among controls ($260/475 = 55\%$).

2. *HART*

Objective. To investigate further the association between talc use and the risk of ovarian cancer.

Methods. Originally, there were 197 cases of women with pathologically confirmed primary epithelial ovarian cancer and 197 hospital controls. These controls had conditions that were not gynecological in nature. Psychiatrically disturbed women, pregnant women, and women with other malignancies were also excluded. The controls were frequency-matched on age, race, and hospital. Information on talc use was obtained on 135 cases and 171 controls.

Results. In the group of women in which no use of talc was mentioned versus the group of women in whom any talc was mentioned, constituting the unexposed and exposed groups respectively, the unadjusted relative risk of ovarian cancer for the exposed to the unexposed groups was 0.76 (95% CI 0.47–1.20). Hence, the hypothesis of no association cannot be

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rejected. Further breakdown of the data indicated that only those women who used diaphragms, as opposed to women who did not use diaphragms, showed an elevated relative risk of ovarian cancer of 1.8 (95% CI 0.7–3.7).

Conclusions. The data do not indicate any association between talc use and risk of ovarian cancer. Furthermore, no dose-response data were given, and no attempt was made to control for potential confounding variables other than the matched variables, age and race, and gravidity. Consequently, little evidence of any association between any reported exposure to talc and an increased risk of ovarian cancer is provided. Finally, it is difficult to evaluate the study on the basis of a one-page report. Factors such as smoking status, weight, and marital status are not addressed in this report.

3. WHIT

Objective. To investigate the roles of blood-borne environmental exposures in ovarian cancer risk, the lifetime consumptions of coffee, tobacco, and alcohol were the principal factors of concern in this case-control study. Furthermore, vaginal exposures to talc and other particulates may present an etiologic hypothesis for the occurrence of epithelial cancer. Thus, the purpose of this study was to investigate these possibilities.

Methods. Women diagnosed with ovarian cancer in the San Francisco Bay Area between 1983 and 1985 and ranging in age from 18 to 74 years provided 188 cases for this study. Matched controls from two control groups, hospital controls and population controls, provided a total of 539 controls. The 280 hospital controls were selected from the same hospitals as the cases, whereas the 259 population controls were selected using random digit dialing. All controls were matched to cases on age, race, and having at least one ovary. Further, hospital controls were excluded if they were admitted for psychiatric, obstetric, gynecological, or malignant conditions. Conditional logistic regression was used to adjust the analysis for confounders.

Results. While this study was designed to examine other potential risk factors, i.e., coffee, tobacco, and alcohol, as well as talc exposure in relation to ovarian cancer, the study did not find evidence of an association between genital talc exposure and an increased risk of ovarian cancer. Women who reported regular use of talc on the perineum showed a marginally significant increase in relative risk, but no other differences were noted between cases and controls when considering other types of perineal talc exposure either alone or taken in combination. The crude relative risk of ovarian cancer for women with any perineal exposure, as opposed to women with no perineal exposure, was 1.19 (95% CI 0.85–1.66). Adjusted for parity, the relative risk became 1.40 (95% CI 0.98–1.99). Other calculated relative risks failed to produce any significant associations.

Conclusions. The study neither indicts nor exonerates talc as a potential ovarian carcinogen. However, several sources of bias were mentioned. These include (1) failure to interview all

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eligible ovarian cancer cases and a completely random sample of controls, (2) the potential pitfalls in combining hospital and population controls, (3) random error in reported talc use that tends to attenuate relative risk estimates, and (4) confounding by differential talc use among women with characteristics predictive of ovarian cancer. This last concern is a very important possible confounder that may be difficult to factor out in any future case-control study. If this issue is to be addressed, then a prospective cohort study should be designed that measures hormone levels at baseline; to our knowledge, however, no such study is underway.

4. *BOOT*

Objective. To study via case-control methodology the various potential risk factors for ovarian cancer, which include infertility, oral contraceptive use, parity, age at menopause, and genital talc use.

Methods. Women with a diagnosis of ovarian cancer were each age-matched to two hospital controls at 13 hospitals in London and two in Oxford, England. For 63 cases recruited from a London hospital where only cancer patients are treated, controls were selected from other London hospitals. The age range for study subjects was 16–65 years. Excluded from the control group were women with bilateral oophorectomy, as well as women with conditions related to reproductive history or oral contraceptive use. All relative risk estimates were adjusted for age in five-year strata and for social class in six categories. A final total of 235 cases and 451 controls was included in the analysis. Maximum likelihood estimates of relative risk with the corresponding 95% confidence intervals were obtained. Tests for trend were computed by means of logistic regression.

Results. Women using talc weekly showed a higher relative risk for ovarian cancer, 2.0 (95% CI 1.3–3.4), than women using talc on a daily basis, $RR = 1.3$ (95% CI 0.8–1.9). If a trend is operative, then such a reversal is, indeed, curious. Furthermore, there was no significant difference between the percentages of cases and controls who used and kept their diaphragms in talc. The crude relative risk of ovarian cancer for women with any perineal exposure versus those women with no exposure was 1.29 (95% CI 0.92–1.81).

Conclusions. The evidence linking talc use with an increased risk of ovarian cancer remains controversial. While it is true that women who used talc weekly or daily had an increased risk compared to women who used talc less frequently, the reversal between weekly and daily use is unexplained, as is the overall nonsignificant relative risk for women with any perineal exposure, compared to women with no exposure. Overall, the study does not provide a clear indication that perineal use of talc increases the risk of ovarian cancer. The authors indicate a possible selective recall bias, in that women were not asked the length of time of their talc use. It may have been that either a woman's symptoms or her disease-related pelvic examinations led her to recall, selectively, her past frequency of talc use.

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5. HAR1

Objective. To investigate whether perineal application of powder, particularly talc, is associated with an increased risk of serious and mucinous borderline ovarian tumors.

Methods. Women residents of three urban, western Washington state counties, diagnosed as having a serious or mucinous borderline ovarian tumor, were identified from the files of the corresponding population-based cancer reporting system. Cases included Caucasian women whose ages were between 20 and 79 and who were diagnosed during the years 1980–1985. Controls were population-based controls located through random digit dialing. Women who had bilateral oophorectomy were excluded from the study. The final sample contained 116 cases (68% of all eligible cases) and 158 controls (74% of those eligible).

Results. Women who reported any perineal use of dusting powders had an adjusted relative risk of 1.1 (95% CI 0.7–2.1) for developing a borderline ovarian tumor. The adjustment was for age, parity, and use of oral contraceptives. It is interesting to note, however, that the crude relative risk was very close to this adjusted value — 1.07 (95% CI 0.66–1.75). Women who used deodorizing powder with or without baby powder (the only powder reported by women who used a second powder) did show an increased risk of borderline tumor development, i.e., a relative risk of 2.8 (95% CI 1.1–11.7). However, the sample size upon which this result was obtained was very small. No other comparisons were statistically significant.

Conclusions. The elevated risk of borderline ovarian cancer among women who specifically used deodorizing powders could have been due to chance or applicable only to borderline but not malignant ovarian tumors. Although Harlow and Weiss believe that this difference between tumor types is unlikely, more study in this area is certainly warranted. Furthermore, because borderline disease is the focus of this paper, one should be concerned with possible misdiagnosis of disease. If even 5% of women diagnosed with the disease are misdiagnosed, the crude relative risk falls to 0.92 (95% CI 0.51–1.60). That is, even the observed elevation in risk disappears. Finally, the authors note the lack of association among women who used only baby powder, which is known to contain pure talc.

6. HAR2

Objective. To determine whether the use of talc in genital hygiene increases the risk for epithelial ovarian cancer.

Methods. Between July 1984 and September 1989, 394 women between 18 and 74 years old were identified as having been diagnosed with borderline or malignant epithelial ovarian cancer at ten different participating Boston metropolitan hospitals. Among these 394 cases, the final sample for analysis was restricted to 235 Caucasian women confirmed to have the disease by pathological review. Population controls were used and were matched on age (within two years) and were all Caucasian. Those having a bilateral oophorectomy were not allowed as controls. The final control sample totaled 239 women. The influence of

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confounders and effect modifiers was assessed through stratification and subsequent unconditional logistic regression.

Results. Overall, 49% of cases and 39% of controls reported exposure to talc via direct application to the perineum or to undergarment, sanitary napkins, or diaphragms, which yielded a relative risk of 1.5 (95% CI 1.0–2.1). Among women with perineal exposure to talc, the risk was significantly elevated in subgroups of women who applied it directly as body powder, RR = 1.7 (95% CI 1.1–2.7); on a daily basis, RR = 1.8 (95% CI 1.1–3.0); and for more than 10 years, RR = 1.6 (95% CI 1.0–2.7). There was a greater risk for women with more than 10,000 applications while ovulating and with an intact genital tract, RR = 2.8 (95% CI 1.4–5.4). However, this exposure was only found in 14% of women with ovarian cancer.

Conclusions. These data show an association between an increased risk for epithelial ovarian cancer and long-time use of perineal talc. While this study investigated thoroughly the issue of an association with lifetime use of perineal talc and increased risk of epithelial ovarian cancer and demonstrated a small increased risk of the disease, the cause and effect issue remains uncertain for several reasons. One major difficulty is subject recall. Both cases and controls were unable to trace their use of talc to infancy. Thus, total exposure may be higher than reported in both cases and controls. An important potential confounder that was not accounted for in this study was oral contraceptive use. More controls used oral contraceptives than cases and oral contraceptive use was associated with less reported talc exposure. Thus, use of oral contraceptives is a possible strong confounder that, if properly considered, could eliminate any observed effect. Many separate subgroup analyses were performed in an attempt to ascertain whether any perineal talc exposure was associated with an increased risk of ovarian cancer by the subgroup characteristic. For example, women with no more than a high school education showed an elevated relative risk of 1.7 (95% CI 1.1–3.1), but not women with more than a high school education, RR = 1.4 (95% CI 0.9–2.4). Perhaps the most interesting subgroup analysis indicated that women who used talc prior to 1960 were at an increased risk compared to women who reported use exclusively after 1960. This may be because either the latter group of women has had a shorter latency period or because asbestos, a suspected carcinogen, was removed from talcum powders after 1975. In either case, the large number of subgroup analyses, while interesting and important for suggesting future studies, does not produce unequivocal findings.

7. ROSE

Objective. To study the relationship between fiber exposure and the development of epithelial ovarian cancer.

Methods. Cases and controls were ascertained from the Johns Hopkins Hospital between 1981 and 1985. Originally, 140 newly diagnosed cases who met the eligibility criteria were obtained; of these cases, 77 (55%) were included in the study. Controls were inpatient females who were free of gynecological and malignant conditions. Controls were matched to

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cases by age (within five years), race, and date of diagnostic admission (within one year). Finding controls who met all the matching criteria was a difficult task and controls could not be found for each case. Finally, there were 46 matched sets (46 controls), 31 of whom consisted of two cases and one control. Since no matched control was found for 13 cases, they were excluded from the analysis. It should be noted that 91% of cases and 89% of controls were Caucasian.

Results. An increased risk of ovarian cancer was observed for women who used talc on their sanitary napkins. The observed relative risk was 4.79 (95% CI 1.29–17.79). However, among the remaining nine relative risks computed, no other was statistically significant. Importantly, the relative risk was 1.0 (95% CI 0.2–4.0) for women reporting any genital fiber use versus those women who were not so exposed. This relative risk was adjusted for the number of live births. The crude relative risk for this overall exposure characteristic was 0.84 (95% CI 0.27–2.63).

Conclusions. While there seems to be an elevated risk of ovarian cancer in women who used talc on their sanitary napkins, this relationship does not seem to carry over to the other studies (for example, Harlow [1992] does not show an elevated risk in this category). Furthermore, in questioning women as to whether they used powder on their sanitary napkins, the response was either yes or no. Thus, no measure of length of use was used in this comparison. As stated by the authors, further research is needed to either confirm or refute their findings.

8. HANK

Objective. To assess whether tubal ligation and hysterectomy affect subsequent risk of ovarian cancer.

Methods. This cohort study included women who participated in the Nurses' Health Study from 1976 to 1988. After excluding individuals with a history of cancer (except nonmelanoma skin cancer), with one or both ovaries removed, or who were postmenopausal in 1976, a baseline population of 77,544 women accrued a total of 859,791 person-years of follow-up.

Results. While talc use as a risk factor for ovarian cancer was not the primary focus of this study, indirect information indicated that there was no increased risk of ovarian cancer due to talc use.

Conclusions. This study could be used only indirectly to obtain a relative risk comparing ovarian cancer in talc users versus nonusers. Briefly, the method is as follows: First, the risk period (and thus the person-years and number of cases) is halved for the total study population. Then, subtracting the number of cases and person-years for non-talc users from these halved values, the person-years and number of cases are estimated for talc users. The resulting estimate is a relative risk of 0.62 (95% CI 0.38–1.02).

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9. CHEN

Objective. To study whether there is an increased risk of ovarian cancer in relation to a number of reproductive, demographic, and lifestyle variables.

Methods. A Beijing, China, case-control study matched by age 112 pathologically confirmed epithelial ovarian cancer cases to 224 community controls. Risk of ovarian cancer was evaluated in relation to number of full-term pregnancies, number of ovulatory years, mumps virus infection, and exposure in the perineal region to talc-containing products. Conditional logistic regression was used to control for potential effects of confounding from selected variables.

Results. This study, despite some methodological shortcomings, including not being able to ascertain a complete series of ovarian cancer patients, a high rate of loss due to deaths among cases (67 in all), and exclusion of controls with current health problems, shows results not dissimilar to studies elsewhere in the world. In particular, reproductive and demographic similarities were noted. For example, as parity increased, the risk of ovarian cancer appeared to decrease. Use of dusting powder indicated an increased risk of ovarian cancer. However, the relative risk of 3.9 (95% CI 0.9–10.6) was not statistically significant when adjusted for education and parity, and only 12 women in the total sample of 336 used dusting powder.

Conclusions. This study reports an association between the use of dusting powder and an increased risk of ovarian cancer. However, since less than 4% of all women in the study sample reported using dusting powder, and, when adjusted for confounders, the relative risk was not statistically significant, this association should not be considered definitive.

10. TZON

Objective. To study whether there is any association between an increased risk of ovarian cancer and the following factors: analgesics, hair dyes, perineal talc, and tranquilizers.

Methods. A hospital-based case-control study of ovarian cancer was conducted in Athens, Greece, during 1989–1991. Cases included 181 women with histologically confirmed common, malignant, epithelial ovarian tumors. The control group, 200 women in all, were, as the cases, from the greater Athens area and were visitors of patients hospitalized in the same ward and at the same time as the cancer patients. All interviews were conducted by personnel in the two participating hospitals. The relationships were analyzed using logistic regression, controlling for demographic and reproductive variables.

Results. Among the risk factors studied, there was a statistically significant and dose-dependent association between hair dyeing and the risk of ovarian cancer ($p < 0.01$). There was no evidence that perineal application of talc was associated with an increased risk of ovarian cancer; the crude relative risk was 0.90 (95% CI 0.30–2.74). After adjusting for the other principal variables (i.e., analgesics, hair dyes, and tranquilizers) and an assortment of demographic and reproductive variables, the relative risk was 1.05 (95% CI 0.28–3.98).

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Conclusions. This study fails to indict talc as a potential causal agent of ovarian cancer. However, the authors conclude that the results obtained in this study are not inconsistent with the other studies of the association between perineal talc use and the risk of ovarian cancer.

META-ANALYSES

Is it wise to perform a meta-analysis on the available case-control studies? If so, what concerns are there about its interpretation? These issues are addressed in this section. Several articles have dealt with the use of meta-analysis when its application is based on combining results of independent clinical trials as well as independent epidemiological studies. In particular, Huque (1988), Stein (1988) and Fleiss and Gross (1991) express concerns about study-to-study heterogeneity, study-by-exposure interaction when there is evidence of heterogeneity, study biases and confounders, and whether all studies, or merely the published studies, have been considered in the proposed meta-analysis. If, for example, the issue of study bias has not been properly addressed, spurious associations due to small biases may reach statistical significance when the studies are combined, because the sample size, in effect, has increased. As Mantel states, "In any one study, the bias may fail to be great enough to give rise to statistical significance. But with meta-analysis such biases can combine so as to give rise to an overall appearance of statistical significance."¹

Although these perplexing and difficult shortcomings with regard to a meta-analysis of the existing talc exposure and ovarian cancer studies remain, meta-analysis is of some value in addressing whether there is an association, and, if so, how large its order of magnitude may be.

The four meta-analyses performed consider exposure levels as either "exposed" or "unexposed." When considering crude relative risks and both malignant and borderline tumor types, all nine studies were included. Since BOOT and ROSE do not provide adequate adjusted relative risk estimates, they were not used for the meta-analysis of adjusted risks and both tumor types. The analysis of crude risks and malignant tumors used seven of the studies, and the analysis of adjusted risks and malignant tumors could use only five of the studies (see Table 3).

Before performing a meta-analysis, study combinability should be tested using the technique in DerSimonian and Laird (1986). The calculated value of this statistic, Q is compared to percentage points for the chi-square distribution with $n - 1$ degrees of freedom, where n is the number of studies. Thus, in each of the analyses the studies are considered combinable and require no extraordinary weighting scheme for the meta-analysis. All of the meta-analyses produce relative risks greater than 1.0 with confidence intervals just excluding the null value.

¹Mantel, Nathan (1990). Personal communication, American University.

TABLE 3. Results of the Meta-Analyses

Analysis	Studies used	<i>Q</i> (degrees of freedom)	RR (95% CI)
Crude risk, both tumor types	All	11.884 (8)	1.27 (1.09–1.48)
Adjusted risk, both tumor types	CRAM, HART, WHIT, HAR1, HAR2, CHEN, and TZON	9.043 (6)	1.31 (1.08–1.58)
Crude risk, epithelial tumors	HART, WHIT, BOOT, HAR2, ROSE, CHEN, and TZON	7.19 (6)	1.20 (1.01–1.44)
Adjusted risk, epithelial tumors	HART, WHIT, HAR2, CHEN, and TZON	7.598 (4)	1.29 (1.02–1.63)

DISCUSSION

Existing evidence linking talc exposure to an increased risk of ovarian cancer cannot be viewed as scientifically conclusive based on a review of the available epidemiological studies. Only the two studies from Boston report an association for ever-users, and the relative risks in nearly every exposure category in almost all studies have been at 2.0 or lower. Given these rather low relative risks reported in the studies, along with the existing biases and confounders that have not been adjusted for, a claim for an increased risk should be viewed with some suspicion. However, all of the meta-analyses arrive at relative risks greater than 1.0 with 95% confidence intervals excluding the null.

There is limited evidence supporting a dose- or duration-response relationship. HAR2 provides the best data set in this respect but suffers from two weaknesses: exposure time after tubal ligation or hysterectomy was excluded, as were periods of anovulation (when a woman was taking oral contraceptives or was pregnant). Since anovulation periods are known to reduce the risk of ovarian cancer and since these adjustments leave controls with shorter periods of exposure, for the most part, whether such an adjustment should be made is open to question. Also, it appears the reasons for a woman using perineal talc have not been well delineated in any of the studies. This may lead to a differential bias, in that the reason for talc use rather than the talc use itself, may actually be a risk factor for ovarian cancer. Finally, HAR2 indicates that even if perineal talc were a risk factor for ovarian cancer, the latency period is very long, perhaps 30 years or more. In fact, HAR2 provides data suggesting an increased risk of ovarian cancer in women who had been using talc prior to 1960.

As can be observed from the objectives in each of the ten studies considered in the previous section, other important factors are correlated with the incidence of ovarian cancer. For example, lifestyle variables, including coffee, tobacco, and alcohol consumption, were studied by WHIT, whereas TZON studied the effects of analgesics and hair dye along with talc. Reproductive issues were the focus of BOOT and HANK.

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Since confounding is a potential concern in any epidemiological study and is especially troublesome when small risks (i.e., relative risk of 2.0 and below) are considered, these other factors need to be considered very carefully in the study of ovarian cancer. For example, it is generally accepted that low parity and nonuse of oral contraceptives are risk factors for ovarian cancer. Unfortunately, these risk factors were not adjusted for in a consistent manner across the studies considered herein. As an example of this, HAR2 fails to adjust for oral contraceptive use even though oral contraceptive users were found to be less likely to report talc exposure than women who did not use oral contraceptives. In this vein it should be noted that among the ten studies in this review, talc exposure was the primary focus in only four studies — CRAM, HART, HAR1 and HAR2.

Other studies have also reviewed the association of talc use and ovarian cancer, but not in the direct framework of either a case-control or cohort epidemiological study. Some of the more important articles are cited. Wehner et al. (1986) state, "Our study, using state-of-the-art techniques in the most suitable animal model available, failed to provide any evidence for such translocation of measurable quantities ($> \sim 0.5$ mg, depending on the radionuclide, detector system and counting time) of talc." This refers to the translocation of talc particles from the vagina to the oviducts of these animals. Longo and Young (1979) implicate asbestos as a possible risk factor, noting its ban in the production of commercial talcum powder in 1973. They note further that exposure to talc from other sources such as chalk, textiles, and crayons is widespread. Recently, a series of articles concerning ovarian cancer risk was published by the Collaborative Ovarian Cancer Group. In the lead article, Whittemore et al. (1992) acknowledge the lack of evidence implicating talc and state, "Other issues, such as the relation of ovarian cancer risk to exposures to talc, tobacco, alcohol, and coffee, were not addressed because too few of the studies had comparable data on the relevant variables."

Additionally, other factors that have not been studied in conjunction with talc exposure may be associated with an increased incidence of ovarian cancer. Cramer et al. (1989) provide some evidence that implicates lactose as a dietary risk factor and transferase as a genetic risk factor. The issues of selection bias and differential bias are not addressed explicitly in these studies. Hence, it is possible, perhaps even likely, that women who have ovarian cancer will selectively remember using talc whereas controls may not have such a remembrance. Further, if there is some hormone, the presence of which may put women at a higher risk for ovarian cancer, then it may also cause perspiration in the perineal area thereby requiring the use of talc.

Thus, the body of knowledge found in the medical literature does not unequivocally support the hypothesis that talc use by women puts them at an increased risk of ovarian cancer. However, the results of the meta-analyses do suggest the possibility of an increased risk of ovarian cancer due to perineal talc use. Further research in this area is warranted by these results.

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APPENDIX

For each of the case-control studies, a relative risk is estimated. The natural logarithm of the relative risk in a study, denoted y_s , is defined in the following equation:

$$y_s = \ln[p_{s1}(1 - p_{s2})/p_{s2}(1 - p_{s1})]$$

The standard error of y_s is given by the equation

$$se_s = \sqrt{1/[n_{s1}p_{s1}(1 - p_{s1})] + 1/[n_{s2}p_{s2}(1 - p_{s2})]},$$

and the limits of the 95% confidence interval for the relative risk are given by

$$\exp(y_s \pm 1.96se_s).$$

The factor by which y_s is weighted in the classical fixed effect analysis, w_s , is given by

$$w_s = 1/(se_s)^2.$$

The "combinability" of the S studies, i.e., the hypothesis that the S underlying odds ratios are equal, may be tested by referring the DerSimonian-Laird statistic

$$Q = \sum w_s (y_s - \bar{y})^2 \text{ with } \bar{y} = \sum w_s y_s / \sum w_s$$

to percentage points of the chi-square distribution with $S - 1$ degrees of freedom. The relative risk estimate is now given as

$$\overline{RR} = \exp(\bar{y}),$$

and the limits of the 95% confidence interval for the overall relative risk are given by

$$\exp(\bar{y} \pm 1.96/\sqrt{\sum w_s}).$$

This interval will not be symmetric about \overline{RR} .